REMARKS

Claim 6 has been objected to due to a typographical error. The claim has been amended to obviate the objection.

Claims 6-7 have been rejected under 35 U.S.C. §103(a) as being unpatentable over con Borstel et al., U.S. Patent No. 5,583,117.

The Examiner's rejection is respectfully travers ed.

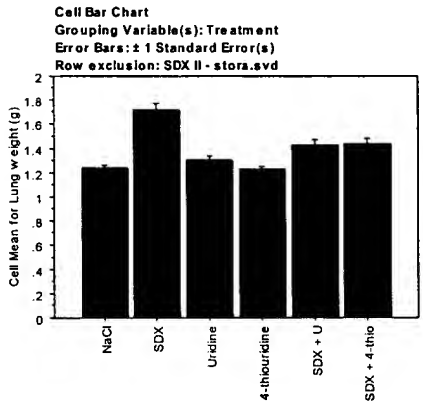
The Applicant's invention is directed to the inhibition of specific cell adhesions and modulation of cell quantity and behaviour of neutrophils and eosinophils by the application of exogenous isomaltitol, 4-thiouridine or uridine. The claims as now amended are for a method for treatment of acute or chronic inflammation and/or problems in hemostasis related to platelet function. The method includes a therapeutically effective amount of one of the compounds selected from the group consisting of 4-thiouridine, isomaltitol, and uridine in the preparation of therapeutically effective compositions against acute or chronic inflammation.

The Applicant's invention is unrelated to the discoveries described by von Borstel *et al* '117. The pathogenesis of a number of inflammatory diseases involves migration of leukocytes, more specifically neutrophils and eosinophils, from blood vessels. The emigration of white blood cells to inflammatory sites requires at least four steps: leukocyte rolling along activated endothelium, leukocyte activation, firm adhesion and transendothelial migration. The Applicant does not believe that it would not be obvious to one skilled in the art, nor indeed experts in the field, that a compound functioning within the cell nucleus should also function to modulate interactions of molecules at the cell surface in the specific inhibition of binding and extracellular interactions of individual cell-types.

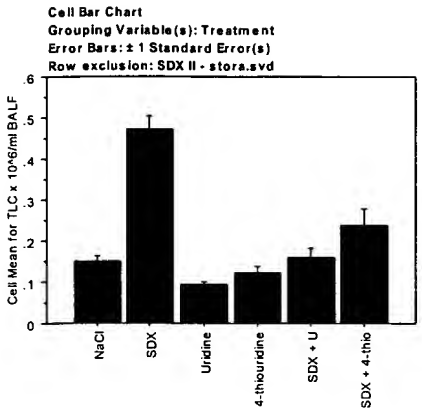
The examiner cites von Borstel et al. '117 (column 17, lines 3-7 and lines 44-53; column 18, lines 34-49) as teaching that exogenous uridine and cytidine are useful in treating conditions such as diabetes and arteriosclerosis and that it would be prima facie obvious to a person skilled in the art to administer exogenous uridine to treat acute and chronic inflammatory conditions. The references included in the Information Disclosure Statement, which are directed to the prior art that one skilled in the art would be aware of, make no mention of inflammation *per se*, but instead describe the use of uridine and cytidine to repair tissue damage associated with these diseases which results from perturbed cellular metabolism and reduced cellular pyrimidine levels. It is not the intention of the Applicant to use any of these substances as a treatment for diabetes itself, but to prevent and treat inflammation by abrogation of cell adhesion. Patients suffering from diabetes may also suffer from additional inflammatory disorders, for example, dermatological inflammations such as acne or psoriasis, unrelated to diabetes but relevant to treatment by inhibition of cell adhesion

The discoveries of von Borstel *et al* '117 are based on the administration of substances which improve the natural repair processes occurring in the nucleus of cells following cell or tissue damage. These processes include; DNA damage repair, (in the case of uridine, transcription-coupled repair processes occurring in conjunction with RNA synthesis, as uridine is not incorporated into DNA), cell metabolism anomalies and RNA biosynthesis. Central to this mechanism of action of exogenous uridine application, or acylated derivatives thereof, is the hexose monophosphate pathway of glucose metabolism which produces pentose sugars. This is a rate limiting step in the synthesis of nucleotides and nucleosides for incorporation into nucleic acids as the availability of pentose sugars/ribose determines the downstream rates of tissue regeneration repair and cellular proliferation.

Screening of various chemical entities resulted in the serendipitous discovery by the Applicant that three compounds, isomalitol, uridine and 4-Thiouridine, could affect adhesion of neutrophils to activated endothelial cells and modulate leukocyte extravasation. These substances therefore affect the genesis of inflammation and achieve a selective modulation of the immune system with the potential advantage of less risk of general immunosuppression. Taking into consideration the complexity of disease patterns and the fact that adhesion molecules were only cloned recently, it would be impossible for even an expert skilled in the art to leap to the conclusion from von Borstel's use of uridine in assisting cellular repair functions, that uridine would specifically, for example, reduce the extravastion of eosinophils in lungs. Figure 1A and 1B illustrate *in vivo* results obtained by the inventor using a sephadex (SDX)-induced rat model of lunginflammation. In this model, increased lung weight and increased number of leukocytes in lung lavage fluid are used as indicative markers of inflammation.



1A. Measurement of lung weight. The increase in lung weight induced by SDX is reversed almost to the level seen in the negative control rats (rats treated with saline (NaCl)) by co-administration of SDX and uridine or 4-thiouridine.

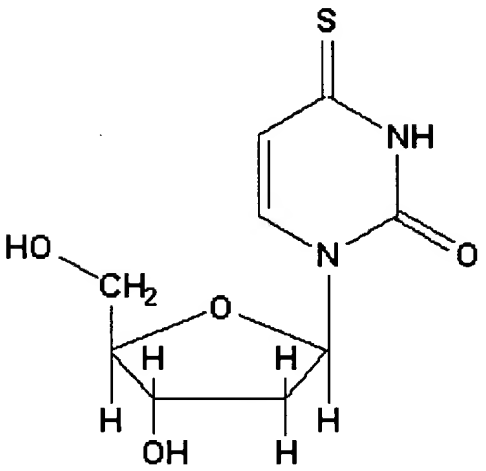


1B. Measurement of leukocytes in lung lavage fluid. The increase in number of leukocytes induced by SDX is reversed almost to the level seen in the negative control rats (rats treated with saline (NaCl)) by co-administration of SDX and 4-thiouridine. Leukocyte levels in the rats co-treated by SDX and uridine were very close to levels seen in saline treated rats.

Also, in contrast to the discoveries of von Borstel *et al,* the prevention and treatment of inflammation discovered by the inventor differs as von Borstel' s application of substance is intended to increase rates of cellular proliferation while the discovery and application of substances by the inventor are intended to reduce extravasation.

The inventions of von Borstel *et al* are dependent on administration of uridine and cytidine derivatives which can be transported across the gastrointestinal tract, blood-brain barrier and other biological membranes, in order to deliver biologically active substance to the cell nucleus. It is documented that the biological properties of unmodified uridine result in it being poorly absorbed following oral administration (noted in von Borstel 6,329,350 column 3, lines 41-59). This provides further indication of the differences in use and effects of uridine between von Borstel and the Applicant.

The biological properties of 4-thiouridine are not addressed at all by von Borstel and previous publications illustrate that this substance cannot be assumed to be analogous in function to uridine.



4-Thiouridine

Due to the presence of sulphur in 4-thiouridine, disulphide bridges can be formed with other 4-thiouridine molecules and other sulphur containing molecules. 4-thiouridine can also be incorporated into RNA. Incorporation of 4-thiouridine however, into newly synthesised RNA molecules in the presence of light in near UV wavelengths has been documented to result in cross-linking of 4-thiouridine, which in turn results in cell-cycle arrest and subsequent tissue damage. This clearly illustrates that a reduction to practice of the invention of von Borstel using 4-thiouridine would result in the opposite effect to that intended.

Additional differences in the chemical properties of uridine and 4-thiouridine are also illustrated by the presence and behaviour of these molecules in tRNAs. The nucleoside 4-thiouridine is naturally occurring in the tRNA of some bacterial strains and is known to mediate near-UV cell killing. In Escherichia coli cells, the 4-thiouridine chromaphore absorbs

light at 340 nm and leads to the cross-linking of up to 50% of bulk tRNA molecules, triggering growth and cell division delay. Specific post-transcriptional modifications such as cyanoethylation and acrylonitrilation also occur in the case of 4-thiouridine. These modifications do not affect uridine.

The above examples clearly show that the use of 4-thiouridine, therefore, to treat inflammation through inhibition of cell adhesion must be considered independently from the use of uridine, as administration of these compounds is not equivalent. Further evidence that 4-thiouridine does not function in an identical manner to uridine is that different quantitative effects are observed between uridine and 4-thiouridine in inhibition of adhesion in a cell type-specific manner (see Figure 1B).

As independent claim 6 is patently distinguishable from the prior art references, the remaining claims dependent therefrom are also patently distinguishable.

In view of the foregoing, it is believed that the amended claims and the claims dependent there from are in proper form. The Applicants respectfully contend that the teachings of von Borstel et al. '117 does not establish a *prima facie* case of obviousness under the provisions of 35 U.S.C. §103(a). Thus, claims 6 and 7 are considered to be patently distinguishable over the prior art of record.

The application is now considered to be in condition for allowance, and an early indication of same is earnestly solicited.

Respectfully submitted,

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